Whole-exome sequencing identifies somatic mutations of BCOR in acute myeloid leukemia with normal karyotype

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1. This work was presented in part by B.F. at the joint Japanese Society of Hematology (JSH)/European Hematology Association (EHA) Symposium during the EHA Congress in London, June 11, 2011.

Abstract

Among acute myeloid leukemia (AML) patients with a normal karyotype (CN-AML), NPM1 and CEBPA mutations define World Health Organization 2008 provisional entities accounting for approximately 60% of patients, but the remaining 40% are molecularly poorly characterized. Using whole-exome sequencing of one CN-AML patient lacking mutations in NPM1, CEBPA, FLT3-ITD, IDH1, and MLL-PTD, we newly identified a clonal somatic mutation in BCOR (BCOR 3'UTR corepressor), a gene located on chromosome Xp11.4. Further analyses of 553 AML patients showed that BCOR mutations occurred in 3.8% of unselected CN-AML patients and represented a substantial fraction (17.1%) of remaining 40% are molecularly poorly characterized. Using whole-exome sequencing of one CN-AML patient lacking mutations in NPM1, CEBPA, FLT3-ITD, IDH1, and MLL-PTD, we newly identified a clonal somatic mutation in BCOR (BCOR 3'UTR corepressor), a gene located on chromosome Xp11.4. Further analyses of 553 AML patients showed that BCOR mutations occurred in 3.8% of unselected CN-AML patients and represented a substantial fraction (17.1%) of CN-AML patients showing the same genotype as the AML index patient subjected to whole-exome sequencing. BCOR somatic mutations were: (1) disruptive events similar to the germline BCOR mutations causing the oculo-facio-cardio-dental genetic syndrome; (2) associated with decreased BCOR mRNA levels, absence of full-length BCOR, and absent or low expression of a truncated BCOR protein; (3) virtually mutually exclusive with NPM1 mutations; and (4) frequently associated with DNMT3A mutations, suggesting cooperativity among these genetic alterations. Finally, BCOR mutations tended to be associated with an inferior outcome in a cohort of 422 CN-AML patients (25.6% vs 56.7% overall survival at 2 years; P = .032). Our results for the first time implicate BCOR in CN-AML pathogenesis.

Submitted July 7, 2011.
Accepted October 11, 2011.

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